



ORIGINAL ARTICLE

Correlation of Plasma Level of Insulin-Like Growth Factor-1 (IGF-1) with Bacterial Index on Leprosy Patients in Bali

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Background: Leprosy is an infection by *Mycobacterium leprae*, which influenced by cellular immunity. Leprosy tends to occur in low socio-economic and nutrition groups. Researchers try to prove the role of nutrition in the pathogenesis of leprosy. Insulin-like growth factor-1 (IGF-1) as a marker of nutritional status shown to play a role in cellular immunity.

Objective: To evaluate the correlation between IGF-1 with bacterial index (BI) on leprosy patients in Bali. **Methods:** Cross-sectional study in Sanglah Public General Hospital, Denpasar of patients with paucibacillary (PB) and multi-bacillary (MB) leprosy were assessed for BI using slit-skin smear. All patients were tested for plasma IGF-1 using chemiluminescent immunometric assay Immulite. All data were analyzed using IBM SPSS ver. 24.0. The study has been approved by local Institutional Review Board with ethical clearance number 2017.02.1.0356. **Results:** Our study involved 44 MB and 2 PB leprosy. The common age group affected was between 31 ~ 40 years old (23.9%), male (60.9%), and normal body mass index (BMI) (65.2%). Mean plasma IGF-1 level in PB leprosy was higher (91.07 ± 0.74 ng/ml) than MB (82.74 ± 6.44 ng/ml). The mean IGF-1 level decreases as BI

increases in both groups (CI 95% = 81.16 ~ 85.04; $p < 0.001$). Pearson correlation test shows strong negative correlation (Pearson $r = -0.976$; $p < 0.001$) with determinant coefficient (R_2) showing 95.2% ($p < 0.001$). **Conclusion:** In Balinese leprosy patients, severity of disease status measured by BI were found to be strongly correlated with the plasma IGF-1 level which may help preventing transmission in household contacts by improving nutritional status. (**Ann Dermatol 32(5) 370 ~ 374, 2020**)

-Keywords-

Bacterial index, Insulin like growth factor 1, Leprosy

INTRODUCTION

Leprosy is a chronic infectious disease, which remains a problem especially in developing countries. Social stigma of leprosy plays a role in low case findings in several countries¹. Until 2016, Indonesia still holds rank three as the country with the most new case findings, after India and Brazil with 17.202 new cases². According to the report from Bali Provincial Health Department in 2013 found 84 new case of leprosy, mainly multibacillary type³. The infection of *Mycobacterium leprae* influenced by virulence factors of bacteria and host factors, which comprise of genetic and immune factors. Cellular immunity status of individuals contributes to the disease status of leprosy patients. Epithelial integration, immunoglobulin A (IgA), natural killer (NK) cell, cytotoxic T-lymphocyte and macrophage are the first barrier which protect the body from *M. leprae* infection⁴. This immune response against leprosy is expressed on macrophage through 4 pathways, the

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toll-like receptor 1 and 2 (TLR1/2) pathway, the tumor growth factor β (TGF- β) pathway, the tumor necrosis factor α (TNF- α) pathway and vitamin D receptor pathway⁵. The high incidence of leprosy on low socio-economic group could express the possible role of nutrition in the pathogenesis of leprosy. A study done by Wagenaar et al.⁶ in Bangladesh showed the high prevalence of leprosy in group with lack of food materials and on malnutrition group. These groups also showed the low consumption of high protein meat and fish. Other study by Fontana et al.⁷ and Livingstone provided that Insulin-like growth factor-1 (IGF-1) level decreases on individuals who consume low protein and calories food compared to the normal population⁸.

Association between immune system and neuroendocrine system had been proven to play a role in homeostasis of host adaptive response to stress and infection. Study done by Smith⁹ and Rodrigues et al.¹⁰ support this on leprosy patients where IGF-1 affect the macrophage through the TNF- α pathway.

This study was done to see the change of IGF-1 plasma level in leprosy patients may influence the status disease shown by the change in bacterial index examination.

MATERIALS AND METHODS

This study was a cross-sectional analysis of 46 leprosy patients attending our Leprosy Subdivision polyclinic over a period of 3 months. The patients were evaluated according to clinical examination and slit skin smear for bacterial index examination. The patient were asked to fill the informed consent and this study has been approved by the local Institutional Review Board (IRB) with ethical clearance number of 2017.02.1.0356.

Blood samples were collected from all leprosy patients, provided that all subjects fulfill the inclusion and exclusion criteria. We excluded patients who were taking corticosteroid, non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraception or who have finished anti-leprotic treatment, which can alter the result of this study. The plasma blood was collected in sterile test tubes and was measured for IGF-1 using chemiluminescent immunometric assay kit (Immulite; Siemens Healthineers, Erlangen, Germany) which follows the World Health Organization International Reference Reagent (WHO-IRR).

Statistical analysis was done using IBM SPSS Statistics for Macintosh (Stratified Program for Social Science) ver. 24.0 (IBM Corp., Armonk, NY, USA). Unpaired t-test was used to measure the comparison. Pearson correlation was used to measure the correlation between the quantitative variables. The data with p -value < 0.05 was considered signifi-

cant.

RESULTS

This study included 46 leprotic subjects consisting of 44 multibacillary (MB) type leprosy and 2 paucibacillary (PB) type leprosy. There were 28 male subjects (60.9%) and 18 female subjects (39.1%) involved in this study with age ranged from 11 to 70 years old (mean \pm standard deviation [SD] = 42.85 \pm 16.10). Slit skin smear examination was negative or bacterial index of 0 in 9 subjects (19.6%) with the mean on all subjects 3.22 \pm 1.78 ng/ml. Leprosy subjects in this study were more in the normal body mass index (BMI) group (65.2%) compared to the obesity group (2.2%). The characteristic of subjects can be seen in (Table 1).

Leprosy subjects showed significantly lower IGF-1 plasma level (83.10 \pm 6.52 ng/ml) compared to the normal range on Immulite (150 ~ 400 ng/ml). On comparing IGF-1 plasma level according to the BMI group, the obese group shows lower level (72.83 ng/ml) than the normal group (83.55 \pm 6.10 ng/ml) (Table 2). The MB leprosy subjects

Table 1. Distribution of subjects by age, sex, body mass index (BMI), leprosy type, and bacterial index (BI)

Variable/category	Value
Age group (yr)	
11 ~ 20	2 (4.3)
21 ~ 30	10 (21.7)
31 ~ 40	11 (23.9)
41 ~ 50	5 (10.9)
51 ~ 60	8 (17.4)
61 ~ 70	10 (21.7)
Sex	
Male	28 (60.9)
Female	18 (39.1)
BMI	
Underweight (< 18.5 kg/m ²)	0 (0)
Normal (18.5 ~ 22.9 kg/m ²)	30 (65.2)
Overweight (23 ~ 24.9 kg/m ²)	7 (15.2)
Pre-obese (25 ~ 29.9 kg/m ²)	8 (17.4)
Obese (\geq 30 kg/m ²)	1 (2.2)
Leprosy type	
Paucibacillary	2 (4.3)
Multibacillary	44 (95.7)
BI	
BI 0	9 (19.6)
BI +1	11 (23.9)
BI +2	6 (13.0)
BI +3	10 (21.7)
BI +4	9 (19.6)
BI +5	1 (2.2)
BI +6	0 (0)

Values are presented as number (%).

Table 2. Comparison of insulin-like growth factor-1 (IGF-1) plasma level based on body mass index (BMI)

BMI	IGF-1 (ng/ml)	p-value
Underweight (<18.5 kg/m ²)	0	0.012*
Normal (18.5~22.9 kg/m ²)	83.55±6.10	
Overweight (23~24.9 kg/m ²)	81.20±7.34	
Pre-obese (25~29.9 kg/m ²)	84.33±7.21	
Obese (≥30 kg/m ²)	72.83	

Values are presented as mean±standard deviation. *Significance being taken at $p < 0.05$.

Table 3. Comparison of insulin-like growth factor-1 (IGF-1) plasma level based on bacterial index

Bacterial index	IGF-1 (ng/ml)	p-value
0	91.93±1.23	<0.001*
+1	87.76±0.94	
+2	81.83±1.73	
+3	79.13±1.59	
+4	75.42±1.24	
+5	68.75	
+6	0	

Values are presented as mean±standard deviation. *Significance being taken at $p < 0.05$.

showed a lower mean level of plasma IGF-1 level (82.74 ± 6.44 ng/ml) than the PB leprosy subjects (91.07 ± 0.74 ng/ml) with statistically significance difference ($p < 0.001$). Regarding the plasma level of IGF-1 on different bacterial index revealed a decrease of IGF-1 plasma level as the bacterial index on skin slit smear increases. The subjects with bacterial index of +5 has the lowest level of plasma IGF-1 (68.75 ng/ml) and subjects with negative (0) bacterial index has the highest level (91.93 ± 1.23 ng/ml) with p -value < 0.001 (Table 3).

Negative correlation was seen between plasma level of IGF-1 and bacterial index, where statistically significant ($r = -0.976$; $p < 0.001$) (Fig. 1). Linear regression was done to identify the strength of bacterial index have on IGF-1 plasma level with coefficient determination of 95.2% ($p < 0.001$).

DISCUSSION

Neuroendocrine involvement in leprosy has shown to play a role in pathogenesis of leprosy, especially from the immune aspect of the disease.

The most common sex affected in our setting is male followed by female with 11 years old as the youngest subject and 70 years old as the oldest (mean 42.85 ± 16.10 years old). This finding is in concordance of the previous work

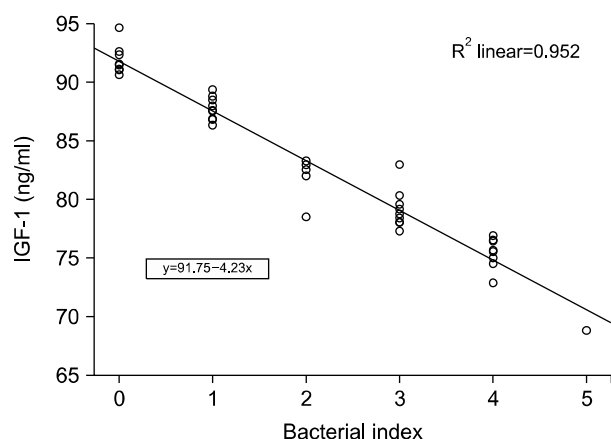


Fig. 1. Correlation of insulin-like growth factor-1 (IGF-1) plasma level and bacterial index.

done by Kumar et al.¹¹ in India with mean age of paucibacillary leprosy 35.1 ± 16.9 years old and MB leprosy 43.3 ± 17.2 years old. Another study done in Brazil found that leprosy tend to happen on adults compare to children below 15 years old, this believed to be caused by the long incubation time of this infection¹². A study done by Varkevisser et al.¹³ in Indonesia, Nigeria, Nepal, and Brazil found similar results with our study where male had higher proportion than female in leprosy subjects. This might be caused by some cultural beliefs that female need permissions by their husbands or families to go to a doctor for examination and also male tend to be more afraid to lose their social and economical status which makes them looking for treatment. Higher mobility and social stigma in those countries may also contribute to the higher case found in male¹³.

This study found that IGF-1 might be influenced by BMI which statistically significant ($p = 0.012$). The obese group has the lowest IGF-1 plasma level at 72.83 ng/ml compared to the normal BMI group. This finding is supported by the study done by Faupel-Badger et al.¹⁴ that found there is a decrease in level IGF-1 with an increase of BMI on Caucasians, dark-skinned and Hispanic groups. The mechanism of this decrease is not clear but there might be a defect on growth hormone secretion on obese patients, which could improve by body weight reduction or growth hormone injection^{15,16}.

The level of IGF-1 is influenced by the nutrition that people took, which might explain the high incidence of leprosy in low income and malnourish groups. This is supported by the clinical study by Gallinetti et al.¹⁷ that found low protein diet, which mainly found on vegetarian group has a lower level of IGF-1. The experimental study on mice also support this data where as the group which given low protein diets compared to the high protein group,

has 35% lower level of IGF-1¹⁸.

This study found that IGF-1 plasma level on MB type leprosy is significantly lower than the PB group ($p < 0.001$). This data is consistent with the decrease of IGF-1 plasma level as the bacterial index increase, which could help in evaluation of disease status of leprosy. In our study subjects with negative (0) bacterial index had the highest IGF-1 plasma level (91.93 ± 1.23 ng/ml) and subject with bacterial index +5 had the lowest (68.75 ng/ml). The correlation Pearson study show a strong correlation between IGF-1 plasma level and bacterial index ($r = -0.976$; $p < 0.001$). This data similar to the study by Rodrigues et al.¹⁹ where borderline lepromatous (BL) and lepromatous leprosy (LL) subjects has significantly lower level of IGF-1 compared to borderline tuberculoid (BT) subjects. The mechanism of how IGF-1 may influenced the bacterial index of leprosy patients is on the effect on cellular immunity. Study by Walsh et al.²⁰ found that IGF-1 could increase level of CD4+ and CD8+ T-cell, help the survival, proliferation, chemotaxis and maturation of T-cell, also prevent T-cell apoptosis. Another study showed the effect of IGF-1 on antibody expression mainly in increasing number of B-cell²¹. Smith⁹ found that not only T-cell and B-cell affected by IGF-1 but also macrophage and granulocyte, which might help explain why subjects with lower IGF-1 plasma level have higher bacterial index, due to the lower status of immunity.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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